UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,141	02/19/2004	Nadine Carozzi	045600/274143	5814

826 7590 07/22/2009

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
KUBELIK, ANNE R	
ART UNIT	PAPER NUMBER
1638	

MAIL DATE	DELIVERY MODE
07/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/782,141	CAROZZI ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/5/08, 3/17/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,19 and 22-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,19 and 22-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-11, 19 and 22-29 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claims 1-11, 19 and 22-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding SEQ ID NO:3 or 5, host cells, plants, plant cells and seeds comprising them, and method of using them to make SEQ ID NO:3 or 5, does not reasonably provide enablement for nucleic acids encoding pesticidal protein with 95% or 90% identity to SEQ ID NO:3 or 5 or nucleic acids with 95% or 90% identity to SEQ ID NO:1, 2 or 4, host cells, plants, plant cells and seeds comprising the nucleic acids, and method of using them to make a pesticidal protein with 95% or 90% identity to SEQ ID NO:3 or 5 and a pesticidal protein encoded by a nucleic acid with 95% or 90% identity to SEQ ID NO:1, 2 or 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection is modified from the rejection set forth in the Office action mailed 4 February 2008, as applied to claims 1-11, 19 and 22-26. Applicant's arguments filed 5 May 2008 have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids encoding a pesticidal protein with 95% or 90% identity to SEQ ID NO:2 or nucleic acids with 95% or 90% identity to SEQ ID NO:1, 2 or

4, host cells, plants, plant cells and seeds comprising the nucleic acids, and method of using them to make a pesticidal protein with 95% or 90% identity to SEQ ID NO:3 or 5 and a pesticidal protein encoded by a nucleic acid with 95% or 90% identity to SEQ ID NO:1, 2 or 4.

The instant specification, however, only discusses sequencing of DNAs from non-publicly available bacterial strain ATX13002 (examples 1-4), identification of a nucleic acid, SEQ ID NO:1, that encodes a protein, AXMI-014, SEQ ID NO:3, with a 55% percent identity to Cry40Aa delta endotoxins and potential alternate start that could encode SEQ ID NO:5 (examples 5-6), assay of the protein for pesticidal activity against *Trichoplusia li* (cabbage loper) (examples 7-8), and prophetic guidance for expression in plants (examples 9-11).

The instant specification fails to provide guidance for how to make the full scope of nucleic acids encoding pesticidal protein with 95% or 90% identity to SEQ ID NO:3 or 5 and nucleic acids with 95% or 90% identity to SEQ ID NO:1, 2 or 4.

Nucleic acids encoding proteins with 90% identity to the 672 amino acid long SEQ ID NO:3 would encode proteins with 67 amino acid substitutions, and nucleic acids encoding proteins with 90% identity to the 669 amino acid long SEQ ID NO:5 would encode proteins with 66 amino acid substitutions. Nucleic acids encoding proteins with 95% identity to SEQ ID NO:3 or 5 would encode proteins with 33 amino acid substitutions.

Nucleic acids with 90% identity to a 2145 nucleotide long nucleic acid like that of SEQ ID NO:1 would have 214 nucleotide substitutions, and thus encompass those that encode proteins with 214 amino acid substitutions relative to SEQ ID NO:3; these proteins would have 70% identity to SEQ ID NO:3. Similarly, nucleic acids with 90% identity to a 2019 nucleotide long nucleic acid like that of SEQ ID NO:2 and a 2010 nucleotide long nucleic acid like that of

SEQ ID NO:4 would have 201 nucleotide substitutions, thus encompassing those that encode proteins with 201 amino acid substitutions. Nucleic acids with 95% identity to a SEQ ID NO:1 would have 107 nucleotide substitutions, and thus encompass those that encode proteins with 107 amino acid substitutions; these proteins would have 85% identity to SEQ ID NO:3. Similarly, nucleic acids with 95% identity to SEQ ID NO:2 or SEQ ID NO:4 would have 100 nucleotide substitutions, thus encompassing those that encode proteins with 100 amino acid substitutions.

The instant specification fails to provide sufficient guidance for which amino acids of SEQ ID NO:3 and 5 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain the activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional protein.

The guidance in the specification with respect to making amino acids substitutions in AXMI-014 is as follows:

The specification teaches that there are generally 5 highly conserved regions among delta-endotoxins, and that these have a similar structure (pg 12, ¶3). The specification teaches the 4 of the 5 highly conserved regions among endotoxins in AXMI-014 (specification pg 4, ¶1); the regions encompass a total of 117 amino acids. The fifth region appears to be missing in AXMI-014.

The specification, in the 4th paragraph on pg 12, says:

> Amino acid substitutions may be made in nonconserved regions that retain function. In general, such substitutions would not be made for conserved amino acid residues, or for amino acid residues residing within a conserved motif, where such residues are essential for protein activity. Examples of residues that are conserved and that may be essential for protein activity include, for example, residues that are identical between all proteins contained in the alignment of Figures 1A, B, and C. Examples of residues that are conserved but that may allow

> conservative amino acid substitutions and still retain activity include, for example, residues that have only conservative substitutions between all proteins contained in the alignment of Figures 1A, B, and C. However, one of skill in the art would understand that functional variants may have minor conserved or nonconserved alterations in the conserved residues.

Conservative substitutions are defined on pg 12, ¶2. A search of the originally filed Fig. 1, shows that there are no positions that are identical among all the proteins in the Figure, and 14 positions that have only conservative substitutions among all the proteins.

The specification also suggests making the claimed nucleic acids by random mutagenesis (pg 13, lines 9-14).

The specification on pg 12, ¶2, suggests that substitutions be made at amino acids that are not essential for biological activity, but does not teach any such amino acids.

Thus, the structural guidance in the specification relies on function.

The specification, on pg 11, ¶2, states:

> Variant proteins encompassed by the present invention are biologically active, that is they continue to possess the desired biological activity of the native protein, that is, retaining pesticidal activity. By "retains activity" is intended that the variant will have at least about 30%, preferably at least about 50%, more preferably at least about 70%, even more preferably at least about 80% of the pesticidal activity of the native protein.

Further, the claims require that the encoded protein have pesticidal activity.

Pests are described in the specification as including, but "not limited to, insects, fungi, bacteria, nematodes, mites, ticks, and the like", with particular interest in insect pests "selected from the orders Coleoptera, Diptera, Hymenoptera, Lepidoptera, Mallophaga, Homoptera, Hemiptera, Orthroptera, Thysanoptera, Dermaptera, Isoptera, Anoplura, Siphonaptera, Trichoptera, *etc.*" (pg 30, ¶2). Thus, "pests" are not limited to plant pests or to insects.

Thus, there would appear be some conflict between the claims' recitation of "pesticidal activity", due to the specification's very broad definition of "pests", and the specification's indication that variant proteins should have the same pesticidal activity as the original protein.

The knowledge in the Cry protein art is as follows:

No *Bacillus Cry* endotoxin has been identified to date that has toxicity all of pests listed in the specification, and none has toxicity to fungi or bacteria or many of the orders listed (see, for example, Bravo et al, 2005, Comprehensive Molecular Insect Science 6:175-205, paragraph spanning pg 176-177). Additionally, many Cry proteins have toxicity only to insects that are not pests for plants, for example, mosquitoes (Bravo et al, pg 177, right column, paragraph 1). Lastly, each *cry* protein only has activity against one or few insect species (de Maagd et al, 1999, Appl. Environ. Microbiol. 65:4369-4374, see pg 4369, column 1, paragraph 1)

Much is known about the structure of Cry proteins, including a crystal structure shared among proteins with little amino acid sequence similarity (Bravo et al, pg 178, right column, paragraph 2).

However, making amino acid substitutions in *cry* proteins is unpredictable.

Aaronson et al (2001, FEMS Microbiol. Lett. 195:1-8) teach that there are extensive functional interactions between the three domains of Cry proteins and that more than one domain is involved in toxin specificity and binding (paragraph spanning the columns on pg 7). de Maagd et al (2001, Trends Genet. 17:193-199) teach that domains II and III are involved in insect specificity (pg 194, right column, paragraph 3) and that domains I and II have coevolved towards certain specificities (pg 196, left column, paragraph 2, and pg 197, left column, paragraph 4). Regions involved in insect toxicity in one Cry protein are not involved in others (Bravo et al, pg 187, right column, paragraph 1).

Even conservative substitutions in nonconserved regions can have unexpected effects on protein function (de Maagd et al, 1999, Figs 2 and 3). A single amino acid substitution in a *cry*

protein may alter its insecticidal specificity, and toxicity must be determined empirically (Tounsi et al, 2003, J. Appl. Microbiol. 95:23-28; see pg 27, column 2, paragraph 2). De Maagd et al (2001) concludes that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2).

Further, even binary proteins, which require interaction with another Cry protein for function, can have the three-domain structure (Jones et al, FASEB J. 2007 21:4112-4120, see paragraph spanning pg 4117-4118). Thus, while much is known about the structure of Cry proteins, relatively little is known about the structures responsible for function.

Point mutations and substitutions of a few amino acids have been made in Cry proteins; however, no one has substituted up to 214 amino acids of a Cry protein, as encompassed the claimed nucleic acids.

From the guidance in the specification, it would appear that the vast majority of the amino acids in SEQ ID NO:3 and 5 could be substituted. However, the teachings discussed above indicate that making 214 amino acid substitutions in a *cry* protein would be unpredictable, if it is even possible.

Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteins that have up to 214 random amino acid substitutions to find those that have pesticidal activity would require undue experimentation.

Further, one of skill in the art could not without undue experimentation make a protein with 214 amino acid substitutions and with *T. li* or lepidopteran pesticidal activity.

AXMI-014 has the most similarity to *cry* proteins with toxicity to mosquito (cry40Aa and cry24Aa; see Ibarra et al, 2003, Appl. Environ. Microbiol. 69:5269-5274; abstract and Table 2). AXMI-014, however, is toxic to the Lepidopteran *T. li*. Thus, one of skill in the art could not use the limited sequence similarity to cry40Aa and cry24Aa as guides for making a *T. li* toxic protein with 214 amino acid substitutions relative to SEQ ID NO:3.

Given the novelty of AXMI-014 and the unpredictability making in amino acid substitutions in *cry* proteins, of one of skill in the art could make a protein with up to 214 amino acid substitutions relative to SEQ ID NO:3, the protein would likely have a very different insect toxicity than AXMI-014. The specification does not teach the insect toxicity of such proteins. Many plants transformed with a nucleic acid encoding a protein that has pesticidal activity as defined in the specification would not be resistant to insects that are pests to plants and/or would not have the structure of a Cry protein. Therefore, one would not know how to use nucleic acids encoding proteins with up to 214 amino acid substitutions relative to SEQ ID NO:3.

Thus, extensive teachings are required for making nucleic acids encoding *Cry* proteins with up to 214 amino acid substitutions relative to SEQ ID NO:3 or 5, as encompassed by the claimed nucleic acids. These teachings are not provided for by the specification. The specification also fails to overcome the unpredictability of making large numbers of amino acid substitutions in *Cry* proteins by providing no working examples of proteins with up to 214 amino acid substitutions relative to AXMI-014.

As the specification does not overcome the unpredictability discussed above by describing the transformation of any plant with a pesticidal protein with 95% or 90% identity to SEQ ID NO:3 or 5, nucleic acids with 95% or 90% identity to SEQ ID NO:1, 2 or 4, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with insect resistance, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges that in *Kubin*, nucleic acids encoding proteins with 80% identity to a sequence identifier were considered enabled in view of the *Wands* factors; the instant claims are drawn to nucleic acids with 90% or 95% identity and as in *Kubin*, the specification teaches show to make variants and calculate the percent identity and assay for activity (response pg 7-8).

This is not found persuasive because nucleic acids with 90% identity to SEQ ID NO:1 encompass those that encode proteins with 70% identity to SEQ ID NO:2, *i.e.*, that have 214 amino acid substitutions in SEQ ID NO:2. The art indicates that even though much is known about Cry protein structure, not enough is known about the structure/function relationship to predict a protein's toxicity. The specification does not teach how to make these proteins.

Applicant urges that the knowledge in the art and the specification provide guidance for make and use the claimed nucleic acids (response pg 8).

This is not found persuasive. There are extensive functional interactions between the three domains of Cry proteins and that more than one domain is involved in toxin specificity and binding (Aaronson et al, paragraph spanning the columns on pg 7). Domains I, II and III are involved in insect specificity (de Maagd et al (2001, pg 194, right column, paragraph 3; pg 196, left column, paragraph 2, and pg 197, left column, paragraph 4). Most importantly, regions involved in insect toxicity in one Cry protein are not involved in others (Bravo et al, pg 187, right column, paragraph 1).

Applicant urges that in the specification the term "pesticidal activity" is not limited to the species against which the parent sequence has activity, but to the level of activity (response pg 8).

This is not found persuasive because a comparison of the level of pesticidal activity requires that the activity be towards the same pest.

Applicant urges that Bravo teaches the role of domain II in receptor binding and recognition, and Jones was able to align Cry49A with other binary proteins (response pg 8-9).

This is not found persuasive. Just because Jones was able to identify Cry49A as a binary protein by alignment does not mean ones was able to deduce to which pests Cry49A would be toxic to by alignment. More than Domain II is involved in receptor binding; further Bravo teaches that regions involved in insect toxicity in one Cry protein are not involved in others (pg 187, right column, paragraph 1).

Applicant urges that although, de Maagd 1999 and 2001, Aaronson, Angsuthanasombat, , Tounsi , and Guo all point to some unpredictability, the majority of the art teaches structure function relationships for this class of proteins (response pg 9). Further, limiting substitutions

only to loops would not allow one to make 214 amino acid substitutions, as there are just not that many amino acids in the loops.

This is not found persuasive because these references teach that interactions between amino acids in Cry proteins is much more complex than can be predicted from guidance suggesting only making conservative substitutions or limiting substitutions to loops. Further, there are no family members for AXMI-014 (SEQ ID NO:2). The instant Table 1 shows that AXMI-014 has the most similarity to *cry* proteins with toxicity to mosquito (cry40Aa and cry24Aa; see Ibarra et al, 2003, Appl. Environ. Microbiol. 69:5269-5274; abstract and Table 2). AXMI-014, however, is toxic to the Lepidopteran *T. li*. Comparison to cry40Aa and cry16Aa would not let one know which amino acids are critical for toxicity toward the Lepidopteran *T. li,* the function of AXMI-014, as cry40Aa and cry16Aa are both mosquito toxins.

4. Claims 1-11, 19 and 22-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action mailed 18 July 2006, as applied to claims 1-11, 19 and 22-23. Applicant's arguments filed 20 November 2006 have been fully considered but they are not persuasive.

The rejection is repeated for the reasons of record as set forth in the Office action mailed 4 February 2008, as applied to claims 1-11, 19 and 22-26. Applicant's arguments filed 5 May 2008 have been fully considered but they are not persuasive.

Nucleic acids encoding a pesticidal protein with 90% or 95% identity to SEQ ID NO:3 and 5 and nucleic acids with 90% or 95%identity to SEQ ID NO:1, 2 or 4, wherein the nucleic acid encodes a pesticidal protein are essential to the operation of the claimed invention. As nucleic acids encoding proteins with 90% identity to SEQ ID NO:3 would encode proteins with 67 amino acid substitutions and nucleic acids with 90% identity to SEQ ID NO:1 encompass those that encode proteins with 214 amino acid substitutions, the claims are drawn to a broad genus of nucleic acids. The level of skill and knowledge in the art at the time of filing was such that no other proteins within the scope of the claims were known.

The specification, on pg 11, ¶2, states:

> Variant proteins encompassed by the present invention are biologically active, that is they continue to possess the desired biological activity of the native protein, that is, retaining pesticidal activity. By "retains activity" is intended that the variant will have at least about 30%, preferably at least about 50%, more preferably at least about 70%, even more preferably at least about 80% of the pesticidal activity of the native protein.

Further, the claims require that the encoded protein have pesticidal activity.

Pests are described in the specification as including, but "not limited to, insects, fungi, bacteria, nematodes, mites, ticks, and the like", with particular interest in insect pests "selected from the orders Coleoptera, Diptera, Hymenoptera, Lepidoptera, Mallophaga, Homoptera, Hemiptera, Orthroptera, Thysanoptera, Dermaptera, Isoptera, Anoplura, Siphonaptera, Trichoptera, *etc.*" (pg 30, ¶2). Thus, "pests" are not limited to plant pests or to insects.

Thus, there would appear be some conflict between the claims' recitation of "pesticidal activity", due to the specification's very broad definition of "pests", and the specification's indication that variant proteins should have the same pesticidal activity as the original protein.

At the time of filing it was known that each cry protein only has activity against one or few insect species (de Maagd et al, 1999, Appl. Environ. Microbiol. 65:4369-4374, see pg 4369, column 1, paragraph 1).

The specification describes no relevant characteristics or motifs for the claimed nucleic acids or the proteins they encode other than identity to SEQ ID NO:1-5 or structures common to all three-domain Cry proteins.

Aaronson et al (2001, FEMS Microbiol. Lett. 195:1-8) teach that there are extensive functional interactions between the three domains of Cry proteins and that more than one domain is involved in toxin specificity and binding (paragraph spanning the columns on pg 7). de Maagd et al (2001, Trends Genet. 17:193-199) teach that domains II and III are involved in insect specificity (pg 194, right column, paragraph 3) and that domains I and II have coevolved towards certain specificities (pg 196, left column, paragraph 2, and pg 197, left column, paragraph 4). Regions involved in insect toxicity in one Cry protein are not involved in others (Bravo et al, pg 187, right column, paragraph 1). de Maagd et al (2001) concludes that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2).

Furthermore, the specification does not describe the structures or amino acids required for the biological activity, *T. li* toxicity, of SEQ ID NO:3, nor does it describe the structural features that distinguish pesticidal protein-encoding nucleic acids with 90% or 95% identity to SEQ ID NO:1, 2 or 4 from other nucleic acids with 90% or 95% identity to SEQ ID NO:1, 2 or 4 or pesticidal proteins with 90% or 95% identity to SEQ ID NO:3 or 5 from other proteins with 90% or 95% identity to SEQ ID NO:3 or 5.

The only species reduced to practice in the specification is SEQ ID NO:1 and 2, which encode SEQ ID NO:3, and fragment SEQ ID NO:4, which encodes SEQ ID NO:5. Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, SEQ ID NO:1 and its subfragments are insufficient to describe the claimed genus.

Hence, Applicant has not, in fact, described nucleic acids encoding a pesticidal protein with 90% or 95%identity to SEQ ID NO:3 or 5 and nucleic acids with 90% or 95%identity to SEQ ID NO:1, 2 or 4, wherein the nucleic acid encodes a pesticidal protein, within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Applicant urges that the instant claims meet the requirements for written description set forth by the Federal Circuit; a given sequence identity is recited, methods for determining the percent identity are known, variants are disclosed, numerous Cry sequences were known in the art, and much was known about Cry protein structure (response pg 10-11).

This is not found persuasive because the structures associated with the claimed function, toxicity toward Lepidopterans, are not known in the art or described in the specification.

Applicant urges that it was known that Cry proteins have three domains, a helix bundle, a three-sheet domain and a beta sandwich motif, citing Li, providing very specific and define

structural parameters to the claimed sequences; four of these domains are in the instant sequence and other teachings in the art describe domain II residues important for toxicity (response pg 11-12).

This is not found persuasive. These general characteristics are true of every Cry protein, including those with toxicity to lepidopterans, coleopterans, nematodes and mosquitoes and those native proteins that do not appear to have any toxicity at all (*e.g.*, cry25Aa). These basic structures are merely characteristics of Cry proteins. They are not specifically associated with the disclosed function, *T. ni* toxicity. de Maagd et al (2001, Trends Genet. 17:193-199) teach that domains II and III are involved in insect specificity (pg 194, right column, paragraph 3) and that domains I and II have coevolved towards certain specificities (pg 196, left column, paragraph 2, and pg 197, left column, paragraph 4). de Maagd et al, 1999, teach that that the crystal structure of Cry1C only allows for limited prediction of the exact structure of Cry1Aa (pg 4373, right column, paragraph 4); thus, Li's teaching is insufficient for describing the structure/function relationship of the claimed nucleic acids. More than the crystal structure and conserved regions are required for Cry protein function. Additionally, it is noted that the claims are not limited to nucleic acids encoding Cry proteins.

Applicant urges individual support for each species is not required; they have provided exemplary nucleotide and amino acid sequences and variants and fragments thereof, and numerous Cry proteins were known in the art, allowing one to envision that claimed invention (response pg 12).

This is not found persuasive because those of skill in the art say that the relationship between structure and function is not well-known in Cry proteins. Aaronson et al, de Maagd et

al, 1999, and de Maagd et al, 2001, make it clear that the correlation between that function and a structure is not sufficiently known in cry proteins as a whole, and the specification does not describe the motifs and amino acids required for SEQ ID NO:2 biological activity. The specification does not make up for this deficit.

Applicant urges that the recitation of a predictable structure is sufficient to satisfy the written description requirement (response pg 12-13).

This is not found persuasive because that is only true if no functional limitations are in the claim. The functional limitation of coleopteran, lepidopteran and heteropteran pesticidal activity requires a description of the structure that confer that activity.

Applicant urges the claims recite functional characteristics that distinguish the claimed sequences, as well as fragments (response pg 13).

This is not found persuasive. The recitation of the function does not describe the structures responsible for it. The relationship between structure and the specific pesticidal function was not described in the specification. SEQ ID NO:3 and 5, which encode 671 and 661 amino acid long fragments, respectively, of the 682 amino acid long SEQ ID NO:2 do not describe proteins with 203 amino acid substitutions relative to SEQ ID NO:2.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 4-7, 24 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ben-Dov et al (1996, Appl. Environ. Microbiol., 62:3140-3145) in view of Carlton et al (1985, Mol. Biol. Microb. Differ., Proc. Intl. Spore Conf., 9th, Meeting date 1984, pages 246-252; Ed. Hoch et al, Am.Soc. Microbiol., Washington, DC) and taken with the evidence of Applicant's response to the Request for Information under 37 CFR 1.105.

Applicant's response to the Request for Information under 37 CFR 1.105, filed 17 March 2009, indicate that the bacterial strain from which SEQ ID NO:1-5 were isolated is HD536, and available from the USDA.

The claims are drawn to a nucleic acid encoding a toxin comprising SEQ ID NO:3 or 5.

Ben-Dov et al teach cloning of delta-endotoxin genes from a *Bacillus thuringiensis* plasmid (pg 3141. left column, to pg 3143, right column, paragraph 3). The genes were cloned in vectors that encode a selectable-marker protein heterologous to the endotoxin, and these clones were grown in an E. coli host cell (pg 3140, right column, paragraph 2). Ben-Dov et al do not teach a nucleic acid encoding a SEQ ID NO:1, 2 or 4.

Carlton et al teach that strain HD536 has a 68 MDa plasmid implicated in toxin production (Table 1).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of cloning delta-endotoxin genes from *B. thuringiensis* plasmids as taught by Ben-Dov et al, to clone delta-endotoxin genes from strain HD536 described in Carlton et al. One of ordinary skill in the art would have been motivated to do so because an increased repertoire of delta-endotoxins would be desirable for increasing toxicity spectra and for overcoming pest resistance to existing endotoxins. It is obvious to use the 68 MDa plasmid from

HD536 because HD536 was known in the art as having a toxin-encoding plasmid (Carlton et al, Table 1). In cloning the toxins from the 68 MDa plasmid from HD536 one of skill in the art would necessarily isolate a nucleic acid encoding SEQ ID NO:3 or 5. It would be obvious to one of skill in the art to culture the host cell comprising the plasmid in conditions under which the nucleic acid encoding the toxins is expressed to study the toxicity of the protein, particularly for toxicity to lepidopteran plant pests.

7. Claims 2-3, 8-11, 19, 22-23, 25-26 and 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ben-Dov et al in view of Carlton et al as applied to claims 1, 4-7, 24 and 27 above, and further in view of Koziel et al (1997, US Patent 5,625,136).

The claims are drawn to plants transformed with a nucleic acid encoding a toxin comprising SEQ ID NO:3 or 5, including plant optimized nucleic acids.

The teachings of Ben-Dov et al in view of Carlton et al are discussed above. Ben-Dov et al in view of Carlton et al do not teach plants and seeds transformed with the nucleic acid.

Koziel et al teach construction of a Cry endotoxin coding sequence that is designed for expression in a plant; this sequence has increased GC content relative to the native coding sequence (column 7, lines 19-56; column 9, lines 50-56). Koziel et al also teach expression of the modified Cry endotoxin coding sequence in maize cells from a victor that also encodes phosphoenolpyrivate carboxylase (column 59, line 40, to column 63, line 50), as well as maize plants and seeds transformed with the modified Cry endotoxin coding sequence (claims 4-25).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to transform the nucleic acid taught by Ben-Dov et al in view of Carlton et al into plants, including maize, as described in Koziel et al. One of ordinary skill in the art would have

been motivated to do so because the resultant plants will be more resistant to insect pests, and the farmer thus less likely to suffer economic loss because of them.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, Ph.D., whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

July 22, 2009

/Anne R Kubelik/
Primary Examiner, Art Unit 1638